tertiary amino groups wherein the tertiary amino groups are selected from -1-piperazinyl and 4-alkyl-1-piperazinyl.

The Amendment of April 19, 2010 was accompanied by a Rule 132 declaration executed by Dr. Jackie Palace (the Palace declaration). In that declaration, Dr. Palace, a physician having extensive knowledge and experience of multiple sclerosis, declares that she does not agree that patients should be prescribed lamotrigine at doses as high as 900mg. Dr. Palace bases this statement on her review of does tolerated in a recent lamotrigine trial in secondary progressive MS, where the highest tolerated dose was 300mg (average only 78mg) in this trial population. The Palace declaration observes that the maximum dose in the recent trial was 400mg which, Dr. Palace notes, was the maximum dose in the Lunardi study.

The attached Giovannoni declaration observes that, prior to the present invention, the recommended daily maximum dosage of lamotrigine (LTG) in the treatment of MS was 400mg daily. Professor Giovannoni notes (paragraph 5) that Lunardi and colleagues treated 15 patients with trigeminal pain with LTG of which 5 patients had MS (patients 16-20). Of the five patients with MS, the highest dose used was 200mg/day (patient 17).

In response to the assertion in the Action that a physician treating MS patients would have considered Bountra and would have taken at face value the statement at page 10, lines 3-7 of Bountra, in regard to dosage levels of LTG, that:

> "A suitable dose is for example 0.1 mg/kg to 30 mg/kg body weight per day calculated as the free base, for example 3 mg/kg to 15 mg/kg. A suitable dose for an adult human is for example in the range of 200mg to 900 mg per day",

Professor Giovannoni declares that in his opinion, at the time of the present invention, an experienced neurologist in this art such as himself would not have contemplated administering LTG to a patient suffering from MS in dosage levels higher than the recommended maximum of 400mg daily. Professor Giovannoni's reasoning (paragraph 8) is that LTG is neuroprotective in animal models of global and focal ischaemia *in vivo* at doses of 20mg/kg and above, i.e., greater than 4X the anticonvulsant dose in rats (although the ED50 is 2mg/kg, the rat anticonvulsant ED95 is approximately 5mg/kg. Professor Giovannoni further states (paragraph 9) that in rat middle cerebral artery occlusion (MCAO) model studies published by Smith and Meldrum in 1995 (*Cerebral protective effect of lamotrigine after focal ischemia in rats,* 1995, Stroke:26,117-122), LTG is only neuroprotective in this model of focal ischemia over a narrow dose range, and that only a dose of 20mg/kg IV significantly reduced neurological scores.

In response to the statement that:

> "Lamotrigine exhibits a bell-shaped dose-response curve for cerebroprotective effect after MCA occlusion in rats. The optimally effective dose is 20mg/kg, which is 10 fold the anticonvulsant dose in rats (anticonvulsant ED50 values against maximal electroshock-induced or sound- induced seizures are 2mg/kg)",

Professor Giovannoni (paragraph 10) notes that doses of LTG (10-50mg/kg) higher than anticonvulsant doses have been used in other studies of global ischemia to achieve neuroprotection in gerbil, rat and pig (see *Lamotrigine: Mechanisms of Action.* Leach, Randall, Stefani and Hainsworth, 2002, In: Antiepileptic Drugs, 5th edition, Eds. Levy, Mattson, Meldrum, Perucca), and that the minimum effective LTG concentration

to block white matter ischaemia *in vitro* is 100uM (*Mechanisms of ischaemic damage to central white matter axons: a quantitative histological analysis using rat optic nerve*, Garthwaite *et al*., Neuroscience, 1999, 94:1219-1230). Professor Giovannoni states that a usual adult maintenance dose for LTG monotherapy of 100-200mg daily with plasma concentrations around 2-4ug/ml (8-16uM) is far lower than concentrations of LTG to reduce white matter axonopathy.

In paragraph 12, the Giovannoni declaration states that doses of LTG lower than 400mg per day have been used to treat central pain in patients with MS, and that in the paper by Leandri and colleagues (*Lamotrigine in trigeminal neuralgia secondary to multiple sclerosis,* Leandri *et al*., 2000. iNeurol. 247:556-558), doses of 25mg daily to a maximum of 400mg daily were used. In paragraph 13, Professor Giovannoni states that pain due to trigeminal neuralgia in patients with MS is usually due to an inflammatory plaque in the root entry zone of the trigeminal nerve and is typically responsive to anti-convulsant medications within the recommended dose ranges, including that for LTG (<400mg per day), and that the indication in this context is for trigeminal neuralgia or pain and **not** neuroprotection, which was not investigated in these studies. Professor Giovannoni further observes that doses that work against central pain syndromes appear to be similar to typical anti-convulsant doses and are typically lower than doses employed for neuroprotection.

In paragraph 16, Professor Giovannoni concludes that, in light of the published facts prior to the present invention and the subsequent US patent filing in 2004, it would not have been obvious to him or any other neurologist with skill in the art of administering LTG that doses higher than the recommended maximum of 400mg daily

could be effective to modify the course of the progressive pathology of MS to the extent exhibited in the patent application.

Based on the above, and the Palace and Giovannoni declarations, it is clear that physicians, post-Bountra, would have interpreted suitable doses as **400mg/day or less**. Neither Bountra nor Lunardi suggests treatment of multiple sclerosis using the claimed dosage level of between 500mg/day and 700mg/day. Thus, taking Bountra alone (or in combination with Lunardi), the physician would **not** have been motivated to arrive at the presently claimed dosage of between 500mg/day and 700mg/day and, in fact, would have acted to reduce the dosage in the case of multiple sclerosis patients based on the state of the art. Reconsideration and withdrawal of the outstanding obviousness rejections are accordingly respectfully requested.

The case was discussed with the Examiner on May 12, 2010, and on May 25, 2010. The Examiner kindly agreed to defer taking the case up for reconsideration until the Giovannoni declaration was in the file. The Examiner's assistance was most appreciated. Favorable action on this application is awaited.

Respectfully submitted,

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